First-order Θ-point of a single polymer chain

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Conformational transitions of a single macromolecule of finite size N cannot be described within standard thermodynamic framework. Taking as a basis a simple model of homopolymer exhibiting a coil-globule transition, we show that a relevant approach is to describe the thermal equilibrium distribution $P_N^{(\beta)}(t)$ of some variable t characterizing the conformation. Although the mean order parameter exhibits a second-order behaviour in the infinite-size limit, the Θ-point arises from the coexistence of two distinct populations, associated with two well-separated peaks of $P_N^{(\beta)}(t)$ and identified respectively with a coil state and a globule state. Remarkably, this first-order feature increases with the size of the chain. It allows to describe the transition within a two-state model, well-suited to analyse experimental data.

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The recent advances of single molecule experiments allow a direct access to the microscopic conformation of a macromolecule at thermal equilibrium [1]. Interpretation of such experimental data requires to stick to a finite-size framework. In particular, a straightforward application of the standard thermodynamic description and classification of phase transitions to conformational transitions of isolated macromolecules of size N is highly questionable. We promote the analysis of the thermal equilibrium distribution $P_N^{(\beta)}(t)$ of some conformational parameter t of the macromolecule. β is as usual equal to $1/k_BT$, where k_B is the Boltzmann constant and T the absolute temperature. We illustrate such a procedure and its motivations on a simple model of coil-globule transition. A main puzzle is the apparent contradiction between the tricritical scaling properties predicted at the Θ-point [2] and the experimental observations [3] of coexistence of two populations with well-separated features, identified with coil and globule states.

In a previous study [4], we evidenced that the relevant order parameter t to unravel the coil-globule transition of an isolated polymer chain of size N with excluded-volume interactions is a power of the density $\rho = Nr^{-3}$, where r is the radius of gyration in a given configuration:

$$t = \rho^{1/(\nu d-1)} = \left(N/r^3\right)^{5/4} \tag{1}$$

(here $d = 3$ and $\nu = 3/5$ is the Flory exponent). The distribution $P_N(t)$ at infinite temperature has been deduced from scaling arguments supplemented with numerical simulations. Choosing an energy $U = -NJt$ where J is some coupling constant, that accounts within a mean-field approximation for attractive interactions at contacts [5], the expression $P_N^{(\beta)}(t)$ for the Boltzmann-Gibbs distribution of the chain is:

$$P_N^{(\beta)}(t) \sim t^c\, e^{-A'(Nt)^{-q}}\, e^{-N[(A-\beta J)t+Bt^n]} \tag{2}$$

A, A', B, c and n are numerical constants fitted on simulation data, with $n \approx 2$ and c undoubtedly lower than -1 ($c \approx -1.13$). We introduce a reduced temperature:

$$\tau = 1 - \theta/T = 1 - \beta J/A \tag{3}$$

For $\tau > 0$, the distribution is strongly peaked around a value of t of order $1/N$. This corresponds to values of r of order N^ν; it leads to identify this high temperature regime with a *coil phase*. For $\tau < 0$, $P_N^{(\beta)}(t)$ is now peaked in the region where t is of order 1. This corresponds to values of r of order $N^{1/d}$ and leads to identify this low temperature regime with a *globule phase*. The temperature $\theta = J/k_BA$ thus gives a rough estimate of the transition temperature.

Focusing on the transition, we investigate more precisely the size and temperature dependence of the distribution $P_N^{(\beta)}(t)$. It involves a scale-invariant factor:

$$h(\hat\tau, \hat t) = \hat t^c e^{-A\hat\tau\hat t - B\hat t^n} \tag{4}$$

where the scaling variables are:

$$\hat t = tN^{1/n} \qquad \text{and} \qquad \hat\tau = \tau N^{1-1/n} \tag{5}$$

The corresponding distribution writes:

$$\hat P_N(\hat\tau, \hat t) = \frac{h(\hat\tau, \hat t)\; e^{-A'N^{-q(1-1/n)}\hat t^{-q}}}{\mathcal{I}_c(N, \hat\tau)} \tag{6}$$

where the normalization factor $\mathcal{I}_c(N, \hat\tau)$, strongly depending on the value of c as we shall see, ensures that $\int_0^\infty \hat P_N(\hat\tau, \hat t)d\hat t = 1$. One might guess at first sight that a scaling regime should be obtained at fixed values of $\hat\tau$ when $N \to \infty$. But due to the value $c < -1$, the limiting function $h(\hat\tau, \hat t) = \hat t^c e^{-A\hat\tau\hat t - B\hat t^n}$ is not integrable in $\hat t = 0$. This obviously compels to focus on the finite-size distribution $\hat P_N(\hat\tau, \hat t)$: the relevance of the size-dependent contribution factor $e^{-A'N^{-q(1-1/n)}\hat t^{-q}}$ in $\mathcal{I}_c(N, \hat\tau)$ breaks the scale invariance. In order to elucidate the influence of the factor $\hat t^c$ on the conformational transition, we shall compare the actual case $c \approx -1.13$ with more general values of c, in particular $c > -1$.

A bimodal shape of $\hat P_N(\hat\tau, \hat t)$ is never observed for $c \geq 0$, neither for $c < 0$ and N smaller than a value $N_0(c) \sim |c|^{-4}$ ($N_0 = 45$ for $c = -1.13$); only one peak exists and it slowly shifts from the coil region towards the globule region as temperature decreases. In this case, represented on Figure 1a, the transition is continuous and no temperature of transition can be clearly defined.

Let us now turn, in all what follows, to the case $c < 0$. For $N \geq N_0(c)$, $P_N^{(\beta)}(t)$ exhibits two peaks in some range of temperatures. Indeed, a globule peak exists for rescaled temperatures $\hat\tau < \hat\tau_g(N)$, where $\hat\tau_g(N)$ slightly decreases from a critical value $\hat\tau_0 = \hat\tau_g(N_0) < 0$ to an asymptotic value $\hat\tau_g(\infty) \sim -|c|^{(n-1)/n}$. The actual value $c = -1.13$ gives $\hat\tau_0 \approx -3.2$ and $\hat\tau_g(\infty) \approx -4$. A coil peak exists as soon as $\tau > \tau_c(N)$ where $\tau_c(N)$ rapidly increases from τ_0 towards an asymptotic value $\tau_c(\infty) < 0$ independent of N (here $\tau_c(\infty) \approx -0.4$). The rescaled bound $|\hat\tau_c|$ thus behaves as $N^{1-1/n}$, so that a coil peak always exists in the scaling region ($\hat\tau$ finite) for N enough large.

The bimodal shape of the single molecule distribution reflects straightforwardly on the statistics describing a dilute solution (enough dilute to neglect interactions between different chains): it indicates that a coil population and a globule population coexist in the interval of rescaled temperatures $[\hat\tau_c(N), \hat\tau_g(N)]$. As represented on Figure 1b, the thermal transition at fixed N is achieved through an exchange of weight between the two peaks. A crucial point is that their positions $\hat t_c$ and $\hat t_g$ remain well-separated when temperature varies: they are located on each side of a value $\hat x(N)$ increasing with N from $\hat x_0$ towards and asymptotic value $\hat x_\infty = [|c|/n(n-1)B]^{1/n}$ (in our case, $\hat x_0 \approx 13$ and $\hat x_\infty \approx 26$). This seems to indicate that our model exhibits a first-order coil-globule

transition [6]. We shall now give a stronger support of this assertion.

A first caveat concerns the experimental reality of the coexistence. It is actually possible to distinguish two populations only if the height of $\hat{P}_N(\hat{\tau},\hat{t})$ at the minimum $\hat{t}_m$ (located between $\hat{t}_c$ and $\hat{t}_g$) differs significantly from the height of the peaks. We have checked that it is true for N enough large. It is then sensible to partition the configuration space in two disjoint "macrostates": a coil state $\{\hat{t} < \hat{x}(N)\}$ and a globule state $\{\hat{t} > \hat{x}(N)\}$ as the peaks remain located on each side of $\hat{x}(N)$ as soon as they exist, even alone. Coexistence is actually observed if the fractions of molecules in each state, i.e. the areas of the two peaks, have comparable values. Let:

$$\kappa(\hat{\tau},N) = \frac{\text{globule peak area}}{\text{coil peak area}} \tag{7}$$

$\kappa(\hat{\tau},N)$ is the equilibrium constant of the transition between the two states and it can be deduced from various experimental data [8]. Such a mapping onto a two-state model relates the theoretical description based on the knowledge of the configurational statistics and the experimental observations through a coarse-graining of the configuration space and not through a thermodynamic limit. The relevance and the validity of this approach will be discussed elsewhere [9]. A keypoint is that the splitting is independent of the temperature and covers the whole configuration space.

Estimation of the contribution of each peak to the total area $\mathcal{I}_c(\hat{\tau},N)$ leads to distinguish two situations. For $c \leq -1$, the coexistence condition $\kappa(\hat{\tau},N) = 1$ writes:

$$\frac{-(1+c)}{2}\ln N = \frac{A^2}{4B}\hat{\tau}^2 + \ln\mathcal{C} + c\ln|\hat{\tau}| \tag{8}$$

where $\mathcal{C}$ is some numerical constant. The coexistence curve $\hat{\tau}_{coex}(N)$ and associated phase diagram is shown in Figure 2. It evidences that coexistence in equal proportions of coil and globule phases is observed only for large enough chains. The shape of the coexistence curve is similar for any $c \leq -1$; $\hat{\tau}_{coex}(N)$ behaves as $\log N$ for large N. The coexistence region has a width $\Delta\hat{\tau} \sim 1/\sqrt{\log N}$: it tends to 0 as $N \to \infty$, so that it makes sense to speak of a "phase transition" in the infinite-size limit [7]. As expected, $\tau_{coex} = \hat{\tau}_{coex}N^{-(1-1/n)}$ tends to 0 as $N \to \infty$, supporting the estimate $\theta = J/k_B A$ of the transition temperature. The shape of the coexistence curve shows that N is not only the size but also a control parameter ruling the transition: increasing N at fixed $\hat{\tau}$ leads into the coil phase.

For $-1 < c < 0$, the coexistence curve is qualitatively different: $\hat{\tau}_{coex}(c,N)$ rapidly tends to a finite negative asymptotic value. Nevertheless, the thermal behaviour at fixed N (enough large) remains unchanged.

In conclusion, for any $c < 0$ and whatever large is N (and $N > N_0(c)$), two populations with distinct features coexist in some range of temperatures; in this respect, the coil-globule transition thus appears as a first-order transition, even in the limit as $N \to \infty$.

Coming back to the unscaled variable t, the minimal distance between the two peaks in the coexistence region satisfies $\Delta t < \hat{x}N^{-(1-1/n)}$, hence tends to 0 as N tends to infinity. The globule density right at the transition point tends to 0 as $\rho_g \sim N^{-2/5}$. This means that in the infinite-size limit, the transition occurs at $\tau = 0$ and coil and globule densities coincide then both to 0. In this respect, this infinite-size coil-globule transition shows some features of a second-order transition, for example the shape of the mean order parameter $< t >$ with respect to the reduced temperature τ has the characteristic shape of a second-order transition, as shown on Figure 3. Nevertheless, the transition occurs through the coexistence of a coil population, whose statistics is controlled only by the size N, and a globule population, whose statistics is scale-invariant and controlled only by the rescaled temperature $\hat{\tau}$, as it can be seen on the location and shape of the corresponding peaks. The first-order nature of the transition originates in the incompatible scale behaviours of the two sets of conformations; hence, it is likely to be observed in some other coil-globule transitions, for enough large chain sizes, as soon as the shape of the distribution $P_N(t)$ (infinite-temperature distribution, describing the purely entropic contribution), gives enough weight to the coil region (here for $c < 0$). A striking signature is the behaviour of the densities along the coexistence curve:

$$\lim_{N\to\infty} \rho_g/\rho_c = (\hat{t}_g/\hat{t}_c)^{4/5} = \infty \tag{9}$$

showing that in fact, the physical difference between the two phases increases with the size N. This first-order nature can be missed in small size but it should appear in the infinite-size description. Moreover, it plays a crucial role in the scaling behaviour of the moments. The first moment writes:

$$< \hat{t} > = \frac{\mathcal{I}_{1+c}(N,\hat{\tau})}{\mathcal{I}_c(N,\hat{\tau})} \tag{10}$$

where

$$\mathcal{I}_{1+c} = \int_0^\infty \hat{t}^{c+1} e^{-A\hat{\tau}\hat{t} - B\hat{t}^n} e^{-A' N^{-q(1-1/n)}\hat{t}^{-q}}\, d\hat{t} \tag{11}$$

Whereas the scaling behaviour of $\mathcal{I}_{1+c}(N,\hat{\tau})$ depends only on the sign of $\hat{\tau}$, the scaling behaviour of $\mathcal{I}_c(N,\hat{\tau})$ differs on each side of the coexistence curve $\hat{\tau}_{coex}(c,N)$ represented on Figure 2. Indeed, the contribution of the globule peak to $\mathcal{I}_c$ is overwhelming on the left-side (i.e. below) of the coexistence curve whereas the contribution of the coil peak is overwhelming on its right-side (i.e. above):

$$\mathcal{I}_c \propto \begin{cases} N^{-(c+1)(1-1/n)} & \text{above} \\ \left(\frac{-A\hat{\tau}}{nB}\right)^{\frac{c}{n-1}} e^{(n-1)B(-A\hat{\tau}/nB)^{\frac{n}{n-1}}} & \text{below} \end{cases} \tag{12}$$

An intermediate scaling region $\hat{\tau}_{coex}(c,N) < \hat{\tau} < 0$ thus appears, where an anomalous tricritical scaling is observed. A detailed presentation of the various scaling regimes following from the first-order nature of the transition will be presented in a following paper [10].

$\hat{P}_N(\hat{\tau},\hat{t})$ actually describes the configurational statistics of the population provided the thermal equilibrium hypothesis is satisfied. This is valid as soon as the system never remains trapped in some region of the configuration space. A practical criterion is to check that there is no bottleneck between the two peaks hence no prohibitory barrier between the associated sets of configurations; a rigorous criterion would require to describe the chain dynamics and is far beyond the scope of the equilibrium picture sketched here.

Although our model of energy is too crude to account for all the details of the actual coil-globule transition, some experimental results support the given picture. Yoshikawa et al. indeed observed the coexistence of coil-like and globule-like conformations in a dilute solution of DNA segments, marked all along their length with fluorescent probes [3]. Such coexistence cannot be accounted for in the standard tricritical picture.

We believe that our example illustrates the different behaviours that may underlie a conformational transition, as those involved in biological functioning. The moral is two-fold:
— in numerical simulations of conformational transitions, the relevant quantity to be studied is the distribution of the order parameter, here $P_N^{\beta}(t)$. Analysis of the moments is not sufficient to reveal the underlying first-order nature of the transition.
— in experimental studies of conformational transitions, the first question to be answered is whether the coexistence of two distinct populations can be observed in some range of temperatures; such an occurence justifies to analyze experimental data within a two-state model. Single molecule observations, now at hand, allow a direct determination of the order parameter distribution; the framework here presented provides a guideline for such novel experimental studies.

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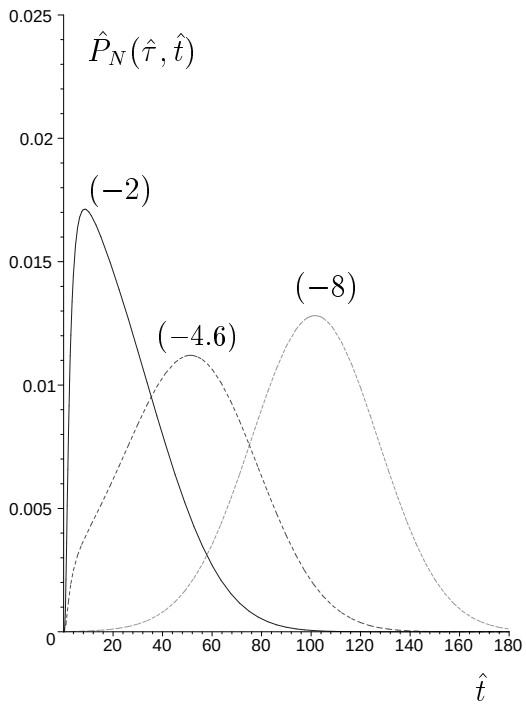
Captions

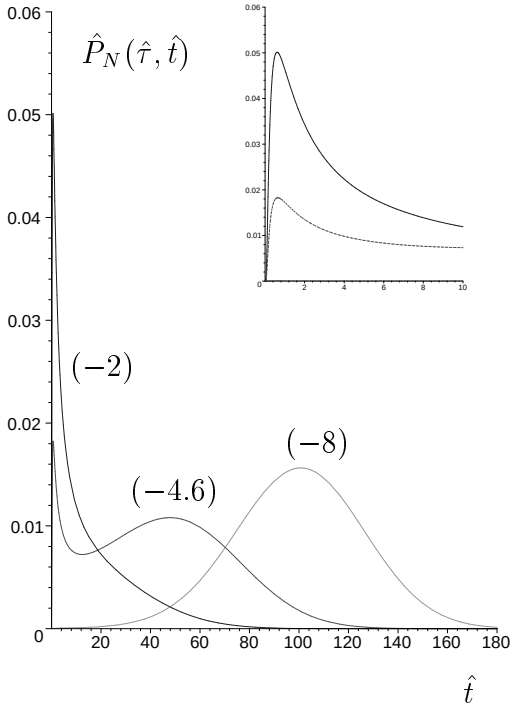
Figure 1:
(a) Continuous transition for small sizes $N < N_0$. Here $N = 20$, $c = -1.13$ and $N_0 = 45$. The evolution of the shape of the graph of $\hat{P}_N(\hat{\tau},\hat{t})$ as the rescaled temperature $\hat{\tau}$ decreases (respectively $\hat{\tau} = -2$, $\hat{\tau} = -4.6$ and $\hat{\tau} = -8$) clearly indicates a continuous transition in which the characteristics of a single population evolves smoothly with $\hat{\tau}$.
(b) Evidence of a first-order transition on the shape of $\hat{P}_N(\hat{\tau},\hat{t})$, plotted with respect to the rescaled variable $\hat{t}$ at fixed N and for various $\hat{\tau}$. Here $N = 2000$ and $c = -1.13$. Curve $\hat{\tau} = -2$: only a coil peak is present. Curve $\hat{\tau} = -8$: only a globule peak is present. Curve $\hat{\tau} = -4.86$: two peaks exist, leading to the coexistence of two distinct populations in dilute solution. The inset shows an enlarged view of the coil region ($\hat{t} < 10$).

Figure 2: Phase diagram in $(\hat{\tau}, \log N)$-space for $c \leq -1$ (here $c = -1.13$). The vertical straight line $\hat{\tau} = \hat{\tau}_g$ bounds above the domain of temperatures where well-identified globule state (a globule peak) exists. The bold curve corresponds to the coexistence in equal proportions of coil and globule populations ($\kappa = 1$ in equation (7)); it behaves as $\sqrt{\log N}$ for large N . The neighbouring curves bound the coexistence region ($\kappa = 10$ on the globule side and $\kappa = 0.1$ on the coil side) of width $\Delta\hat{\tau}(N) \sim 1/\sqrt{\log N}$ for large N. A first-order transition occurs when $\hat{\tau}$ increases at fixed N or when N increases at fixed $\hat{\tau} < \hat{\tau}_g$.

Figure 3: Plot of the average order parameter $< t >$ with respect to the reduced temperature τ for $N = 20$ ($+$), $N = 100$ ($\Box$) and $N = 1000$ ($\diamond$); in the limit as $N \to \infty$, the curve exhibits the typical shape of a second-order transition.


$\hat{P}_N(\hat{\tau},\hat{t})$
(−2)
(−4.6)
(−8)
0.025
0.02
0.015
0.01
0.005
0
20 40 60 80 100 120 140 160 180
$\hat{t}$

(a)


$\hat{P}_N(\hat{\tau},\hat{t})$
(−2)
(−4.6)
(−8)
0.06
0.05
0.04
0.03
0.02
0.01
0
20 40 60 80 100 120 140 160 180
$\hat{t}$

(b)

Figure 1

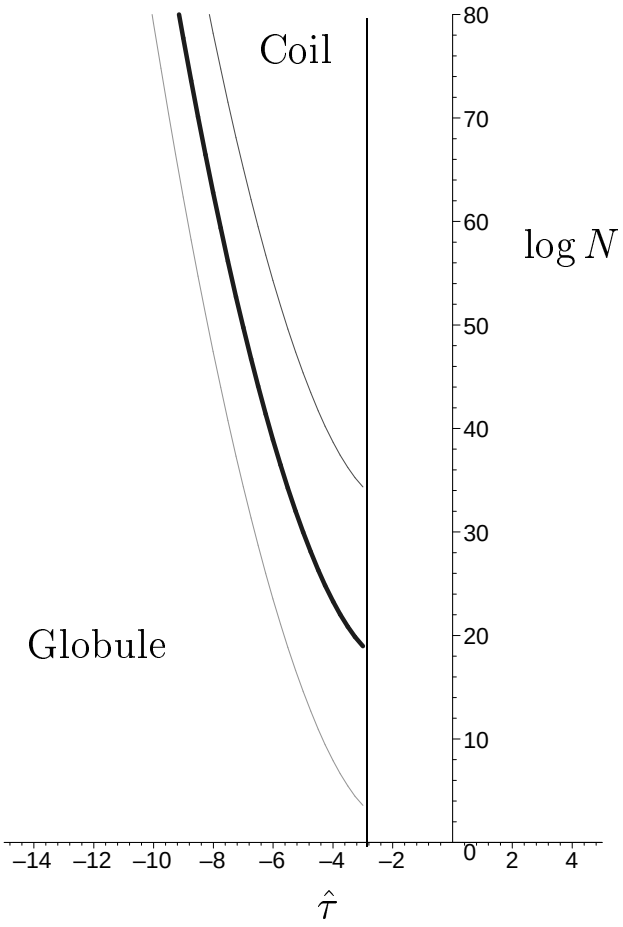

Coil
Globule
log N
80
70
60
50
40
30
20
10
0
−14
−12
−10
−8
−6
−4
−2
2
4
$\hat{\tau}$

Figure 2

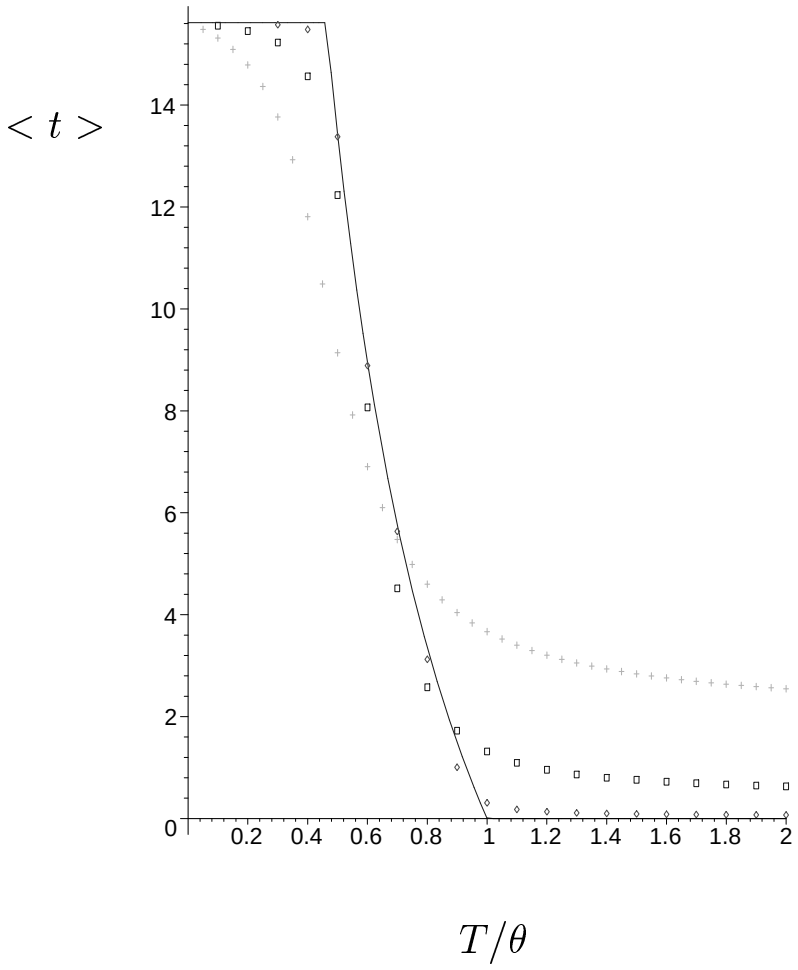


Figure 3